Reports of Practical Oncology and Radiotherapy 25 (2020) 1023–1028

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Characterization of knowledge-based volumetric modulated arc therapy plans created by three different institutions' models for prostate cancer

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ARTICLE INFO

Article history:
Received 12 May 2020
Received in revised form 26 June 2020
Accepted 14 August 2020
Available online 25 August 2020

Keywords:
Knowledge-based planning
RapidPlan
Volumetric modulated arc therapy
Inverse planning
Quality assurance for planning

ABSTRACT

Background: The aim of this study was to clarify factors predicting the performance of knowledge-based planning (KBP) models in volume modulated arc therapy for prostate cancer in terms of sparing the organ at risk (OAR).

Materials and methods: In three institutions, each KBP model was trained by more than 20 library plans (LP) per model. To validate the characterization of each KBP model, 45 validation plans (VP) were calculated by the KBP system. The ratios of overlap between the OAR volume and the planning target volume (PTV) to the whole organ volume ($V_{overlap}/V_{whole}$) were analyzed for each LP and VP. Regression lines between dose–volume parameters (V_{90}, V_{75}, and V_{50}) and $V_{overlap}/V_{whole}$ were evaluated. The mean OAR dose, V_{90}, V_{75}, and V_{50} of LP did not necessarily match those of VP.

Results: In both the rectum and bladder, the dose–volume parameters for VP were strongly correlated with $V_{overlap}/V_{whole}$ at institutes A, B, and C ($R > 0.74$, 0.85, and 0.56, respectively). Except in the rectum at institute B, the slopes of the regression lines for LP corresponded to those for VP. For dose–volume parameters for the rectum, the ratios of slopes of the regression lines in VP to those in LP ranged 0.51–1.26. In the bladder, most ratios were less than 1.0 (mean: 0.77).

Conclusion: For each OAR, each model made distinct dosimetric characterizations in terms of $V_{overlap}/V_{whole}$. The relationship between dose–volume parameters and $V_{overlap}/V_{whole}$ of OARs in LP predicts the KBP models' performance sparing OARs.

1. Introduction

Knowledge-based planning (KBP) was designed to compensate for the weaknesses of inverse planning, in which plan quality depends on planners or institutional skills.[1–7] KBP can provide dose distributions for new patients according to the relationships, dose distributions, and displacements of the target and organs at risk (OARs) at an institution. Formulas to estimate the dose to OARs were derived from the relationship between dose and displacement.[1–3] Moore et al.[3] described KBP as the control of dosimetric variations among calculated plans.

The KBP system named RapidPlan (Varian Medical Systems, Palo Alto, CA, USA) was developed and is utilized in a commercial treatment planning system, Eclipse (Varian). Various deep learning and machine learning (ML) techniques have spread in radiology.[8–12] RapidPlan's ML technique is a supervised model for calculation that is trained with more than 20 cases. In RapidPlan, the objectives are set automatically according to learning plans in the models.[12] Using RapidPlan has provided more stable OAR doses with shorter planning time than manual planning.[7,13–17]

RapidPlan has the advantage of sharing its models among multiple institutions. It has been shown that sharing models between institutions with similar planning designs effectively facilitated

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https://doi.org/10.1016/j.rpor.2020.08.011
1507-1367/

Table 1
Information about each model. Numbers of cases, whole organ volume [cm^3], and ratio of overlap between organ at risk (OAR) and planning target volume to the whole organ volume ($V_{overlap}/V_{whole}$) for library plans (LP) and validation plans (VP) using each model.

OAR		LP			VP
	Institute	A	B	C	
	Case number	20	100	50	45
Rectum	Total volume [cm^3]	42.4 ± 13.0	45.2 ± 14.1	59.7 ± 24.9	44.2 ± 15.4
	$V_{overlap}/V_{whole}$	5.8% ± 2.2%	8.8% ± 3.6%	6.0% ± 2.7%	11.3% ± 6.3%
Bladder	Total volume [cm^3]	98.9 ± 26.8	173.8 ± 101.7	165.1 ± 98.4	160.2 ± 79.4
	$V_{overlap}/V_{whole}$	5.1% ± 2.3%	8.3% ± 4.5%	8.7% ± 3.9%	8.8% ± 6.0%

Table 2
Dosimetric comparison of library plans (LP) and validation plans (VP) in each institution's model.

		A		B		C	
		LP	VP	LP	VP	LP	VP
PTV	D_2	103.0 ± 0.3	102.1 ± 0.5	103.4 ± 0.4	102.4 ± 0.6	105.6 ± 0.8	103.7 ± 0.9
	p val.	**<0.01**		**<0.01**		**<0.01**	
	D_{95}	96.4 ± 0.6	96.9 ± 0.5	96.2 ± 0.3	96.8 ± 0.7	100 ± 0.4	100 ± 0.0
	p val.	**<0.01**		**<0.01**		0.195	
	D_{98}	93.7 ± 1.3	94.7 ± 1.0	92.9 ± 1.5	94.8 ± 1.0	98.8 ± 0.7	99.3 ± 0.3
	p val.	**0.03**		**<0.01**		**<0.01**	
Rectum	V_{50}	21.5 ± 5.5	28.6 ± 10.3	43.6 ± 6.7	40.6 ± 7.0	33.0 ± 7.6	36.7 ± 6.7
	p val.	**<0.01**		**<0.01**		**<0.01**	
	V_{75}	10.9 ± 3.8	19.6 ± 8.9	23.9 ± 4.2	24.0 ± 7.6	15.9 ± 4.0	17.8 ± 4.4
	p val.	**<0.01**		0.625		0.052	
	V_{90}	4.4 ± 1.8	9.5 ± 6.2	14.1 ± 3.0	12.9 ± 5.3	7.9 ± 2.6	8.7 ± 2.6
	p val.	**<0.01**		0.372		0.050	
Bladder	V_{50}	24.2 ± 8.6	34.1 ± 15.0	33.7 ± 14.2	29.2 ± 14.3	41.7 ± 14.8	37.6 ± 16.5
	p val.	**0.03**		0.07		0.188	
	V_{75}	13.6 ± 5.1	18.2 ± 8.5	16.9 ± 7.6	16.4 ± 9.5	23.5 ± 8.5	19.9 ± 9.7
	p val.	**0.017**		0.395		**0.040**	
	V_{90}	8.9 ± 3.4	12.2 ± 6.2	10.9 ± 5.0	11.3 ± 7.1	16.2 ± 5.9	13.8 ± 7.3
	p val.	**0.013**		0.778		**0.043**	

Abbreviations: *PTV* planning target volume, V_{50} volume ratio receiving 50% of the prescribed dose, V_{75} volume ratio receiving 75% of the prescribed dose, V_{90} volume ratio receiving 90% of the prescribed dose, D_2 percentage of the prescribed dose to 2% of the prescribed volume, D_{95} percentage of the prescribed dose to 95% of the prescribed volume, D_{98} percentage of the prescribed dose to 98% of the prescribed volume.

standardization of inverse planning.[18] Because performance of KBP models depends on the model's plan design,[19,20] when planners share KBP models from other institutions with a superior plan design, planners may improve their institutional planning with the KBP system. Thus, planners should test whether the models are suitable for their institutional plan design at least once before sharing them. In addition, verifying the performance of KBP models takes much time because calculating plans for various cases with KBP is required. Thus, predictions of KBP model performance without calculation are necessary. The aim of this study was to clarify factors predicting the performance of KBP models in terms of sparing the OAR. In KBP using RapidPlan, the method of predicting the dose to the OAR with plans being used to train the models was suggested.

2. Methods

2.1. Definitions of structures and prescriptions at each institute

Three institutions (Institutes A, B, and C) were enrolled in this study. These institutes treated patients with T1–T2c prostate cancer using volumetric modulated arc therapy (VMAT). Each institute has different contouring definitions for the clinical target volume (CTV), CTV to the planning target volume (PTV) margin, and rectum. Contouring definitions for the CTV were prostate and proximal 10 mm of seminal vesicle (SV), prostate and proximal half of SV, and prostate and proximal 15 mm of SV in institute A, B, and C. CTV to PTV margin in mm for all around, except posteriorly/posteriorly, are 6/4, 8/6, and 8/5 in institute A, B, and C. Contouring definitions for the rectum are from the rectosigmoid junction to the anus, 1.5 cm above the SV to 1.5 cm below the prostate, and up to 1.0 cm above and below the PTV in institute A, B, and C. The prescription dose was a mean PTV dose of 78 Gy at Institutes A and B and the dose to a volume including 95% (D_{95}) of the PTV minus the rectum at Institute C.

2.2. Each RapidPlan model for calculation of KBP

At each institute, KBP models were created using more than 20 library plans (LP) for each model in the RapidPlan system (Varian Medical Systems, Palo Alto, CA, USA). In each model, LP were clinically used for treatment before April 2017 at each institute. To attain the ideal dose distribution in RapidPlan, the upper objectives were set to decrease the high dose region in the rectum for each institute. For the line objectives, the mean ± SD of priority was 64 ± 0.7, 60 ± 1.6, and 49 ± 2.3 at Institutes A, B, and C, respectively. Each clinically accepted model from all institutes was sent to institute B and imported into the Eclipse there. These models were read from. xml files uploaded to the Varian Model Analytics (https://ModelAnalytics.varian.com) website. The files also contained basic information about the model's LP, such as dose volume histogram (DVH) and the ratio of overlap between OAR volume and PTV to the whole organ volume ($V_{overlap}/V_{whole}$).

2.3. Validation plans for KBP

To validate the performance of 3 kinds of KBP models, 45 cases clinically treated from May 2017 to April 2018 were used with single optimization in Institute B's RapidPlan system. The validation plans (VP) were different from the LP in each model. The CT scanner was Revolution HD (GE Medical Systems, Milwaukee, WI, USA). The

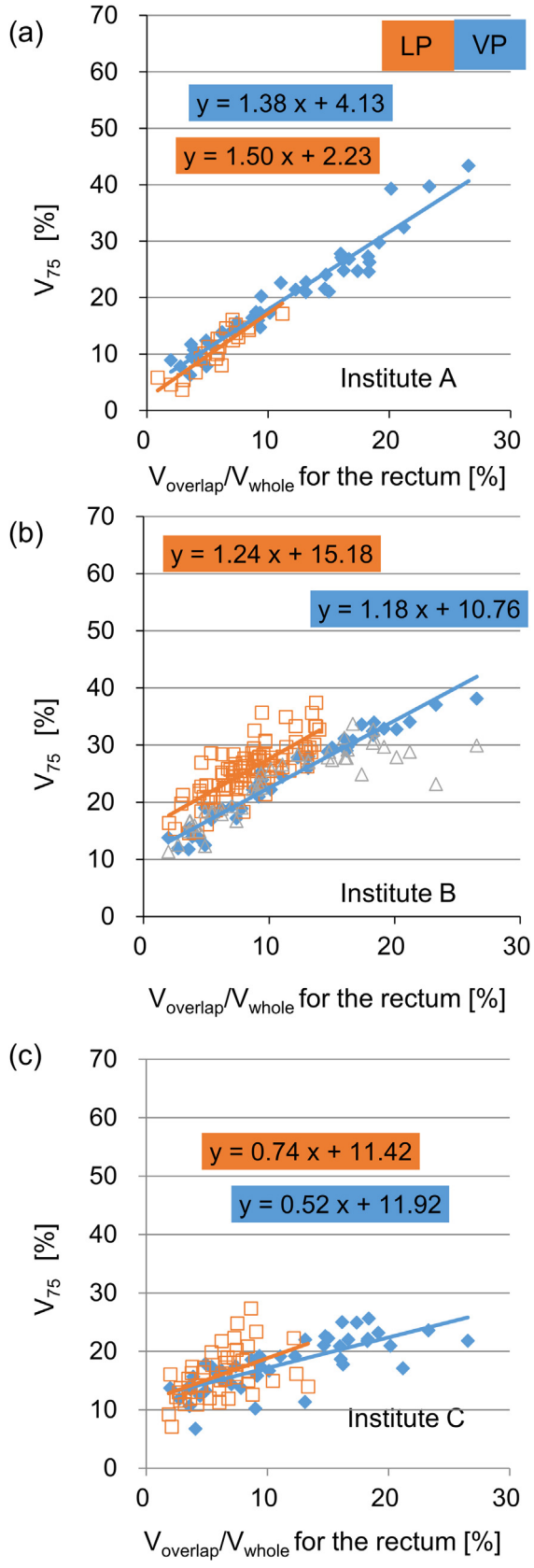

Fig. 1. Relationship between V_{75} and $V_{overlap}/V_{whole}$ of the rectum at institutes A (a), B (b), and C (c). The horizontal axis is $V_{overlap}/V_{whole}$ for the rectum. The vertical axis is V_{75} for the rectum. Blue and orange dots represent the doses in library plans (LP) and validated plans (VP), respectively. Each solid line is a linear regression line between each rectal dose and $V_{overlap}/V_{whole}$ for the rectum. Gray dots represent the doses in manual plans for validated cases.

slice thickness of the CT images was 2 mm, matrix size 512 × 512, and field of view 50 cm.

For these VPs, the following beam conditions were utilized: beam energy 6 MV photons from a TrueBeam linear accelerator equipped with a Millennium 120-leaf multileaf collimator (Varian Medical Systems, Palo Alto CA, USA). The treatment field was 2 full arcs of clockwise rotation from 181◦ to 179◦ and counterclockwise from 179◦ to 181◦. The arcs had collimator rotation of ±30◦, and the optimization and calculation algorithms were Anisotropic Analytical Algorithm and Photon Optimizer 13.0 (Varian Medical Systems, Palo Alto CA, USA). The grid size was 2.5 mm. The prescription setting for VP was the same as that for LP in each institution. Written informed consent was obtained from all patients, and the Institutional Ethics Committee approved this study (Osaka International Cancer Institute Review Board number: 1611119172).

2.4. Data analysis

The dose–volume parameters, represented as a percentage of the prescribed dose to 2%, 95%, and 98% of the prescribed volume (D_{95}, D_{95}, and D_{98}) and the volume ratio receiving 50%, 75%, and 90% of the prescribed dose (V_{50}, V_{75}, and V_{90}, respectively) for the rectum and bladder, were extracted from the DVH data for LP and VP. To evaluate the OAR dose of each model, each dose–volume parameter was sorted by $V_{overlap}/V_{whole}$ in the rectum and bladder. The correlations between dose–volume parameters (V_{50}, V_{75}, and V_{90}) and $V_{overlap}/V_{whole}$ were evaluated using linear regression analysis. The Mann-Whitney *U* test (SPSS 8.0; SPSS, Inc., Chicago, IL) was used to calculate and evaluate the differences between the dose–volume parameters in LP and VP. Values of $p < 0.05$ were defined as significant.

3. Results

3.1. Basic information about cases in the model and validation sets

Table 1 shows basic information about the LP and VP. The model at institute B was trained by the maximum number of plans (i.e., 100 plans). Institute A had the smallest average $V_{overlap}/V_{whole}$ for the rectum and bladder among the three institutions, although the average volume of the rectum and bladder were also the smallest at Institute A. The use of the smallest margin setting at Institute A might have influenced this result. Institute B had the largest $V_{overlap}/V_{whole}$ ratios for the rectum and bladder among the three institutions because institute B had the largest PTV margin.

Table 2 shows dosimetric comparison of LP and VP in each institution's model. In the PTV, there were significant differences between VP and LP, except D_{95} for institute C. In the rectum, at institute A, each dose–volume parameter for VP was significantly larger than that for LP ($p < 0.01$). Institute B and C have significant differences in V_{50} between VP and LP ($p < 0.01$). In the bladder, at institute A, each dose–volume parameter for VP was significantly larger than that for LP ($p < 0.05$). Institute B had no significant differences in any dose–volume parameters between VP and LP. Institute C had significant differences in V_{75} and V_{90} between VP and LP ($p < 0.05$).

3.2. Relationships between dose–volume parameters and $V_{overlap}/V_{whole}$

Fig. 1 shows the relationships between V_{75} and $V_{overlap}/V_{whole}$ for the rectum at institutes A, B, and C. Linear regression lines were drawn between dose–volume parameters and $V_{overlap}/V_{whole}$. For V_{75} at institutes A and C, the slope and height of VP regression lines coincided with those for LP. For V_{75} at institute B, the height

of the VP regression lines was lower than those for LP, although the slope of the regression lines for VP coincided with that for LP. The regression lines for VP ran along the lower boundary of the LP distributions. The manual plans used clinically for VP are shown in Fig. 1 (b). For manual plans in which the rectal $V_{overlap}/V_{whole}$ ratios were large, the rectal dose was reduced so as not to exceed the dose constraints. Therefore, the rectal doses in the manual plans were lower than those of the VP optimized by RapidPlan.

Fig. 2 shows the relationships between V_{75} and $V_{overlap}/V_{whole}$ for the bladder at institutes A, B, and C. At all institutes, the height of the VP regression lines coincided with those for LP. Most of the slopes of the regression lines for VP were smaller than those for LP. The intervals between the regression lines of VP and LP were spread so that the range of $V_{overlap}/V_{whole}$ was large. Manual plans for VP are shown in Fig. 2 (b). The bladder dose in the manual plans was consistent with that for VP in all cases.

Table 3 shows the correlation values between all dosimetric parameters and $V_{overlap}/V_{whole}$ for each OAR in LP and VP for each KBP model. In the rectum, VP for all dosimetric values, except V_{90} at institute A, had higher correlation values than those for LP. At Institutes A and B, all dosimetric values for VP had strong correlation values ($R \geq 0.9$). In the bladder, each dose–volume parameter for VP and LP had strong correlations with $V_{overlap}/V_{whole}$ for each OAR ($R > 0.7$).

Table 4 shows the ratios of slopes of regression lines between all dose–volume parameters and $V_{overlap}/V_{whole}$ for each OAR in LP and VP for each KBP model. The slopes of the regression lines represent the performance of increasing the OAR dose per unit $V_{overlap}/V_{whole}$ in each KBP model. Thus, smaller values were superior at sparing the OAR dose per unit $V_{overlap}/V_{whole}$. The ratio lower than 1.0 means that sparing the OAR dose per unit $V_{overlap}/V_{whole}$ for VP is superior to that for LP. In the rectum, the ratio of the slope in Table 4 ranged 0.51–1.26 (mean: 0.95; ratio >1.0 means higher slopes for VP than LP). In V_{75} for the rectum, sparing the OAR dose per unit $V_{overlap}/V_{whole}$ for VP is improved compared with that for LP in each institute's model.

4. Discussion

In this study, characterizations of LP and VP at three institutions with different plan designs and contouring definitions were analyzed in terms of the $V_{overlap}/V_{whole}$ of two OARs: the rectum and bladder. Strong correlations between $V_{overlap}/V_{whole}$ and OAR dose were observed in three KBP models. The strong correlation between $V_{overlap}/V_{whole}$ and OAR dose in KBP has already been described[3,19]; however, few reports have mentioned the relationship between LP and VP in KBP. The regression lines between dosimetric parameters and $V_{overlap}/V_{whole}$ of the rectum in LP coincided with the regression lines in VP, except those for the rectum at institute B.

The previous report described that estimated OAR dose in LP had strong correlation with $V_{overlap}/V_{whole}$ in multiple centers.[19] They could not create the relationships between OAR dose calculated with RapidPlan and $V_{overlap}/V_{whole}$ in VP because there were two VPs. In this study, 45 plans were calculated with RapidPlan for validations in each model. Therefore, we can compare regression curves between OAR dose and $V_{overlap}/V_{whole}$ in LP and VP. We found that the relationship between dose–volume parameters and $V_{overlap}/V_{whole}$ of OARs in LP predicted the KBP models' performance without dependencies on the number of LP and range of $V_{overlap}/V_{whole}$. In contrast, the manual plans did not show correlations between dose–volume parameters and $V_{overlap}/V_{whole}$, as shown in Figs. 1 and 2. Therefore, this methodology can be applied for all users. The results of this study indicated that users should select plans to train models with dosimetric analysis when they create KBP models.

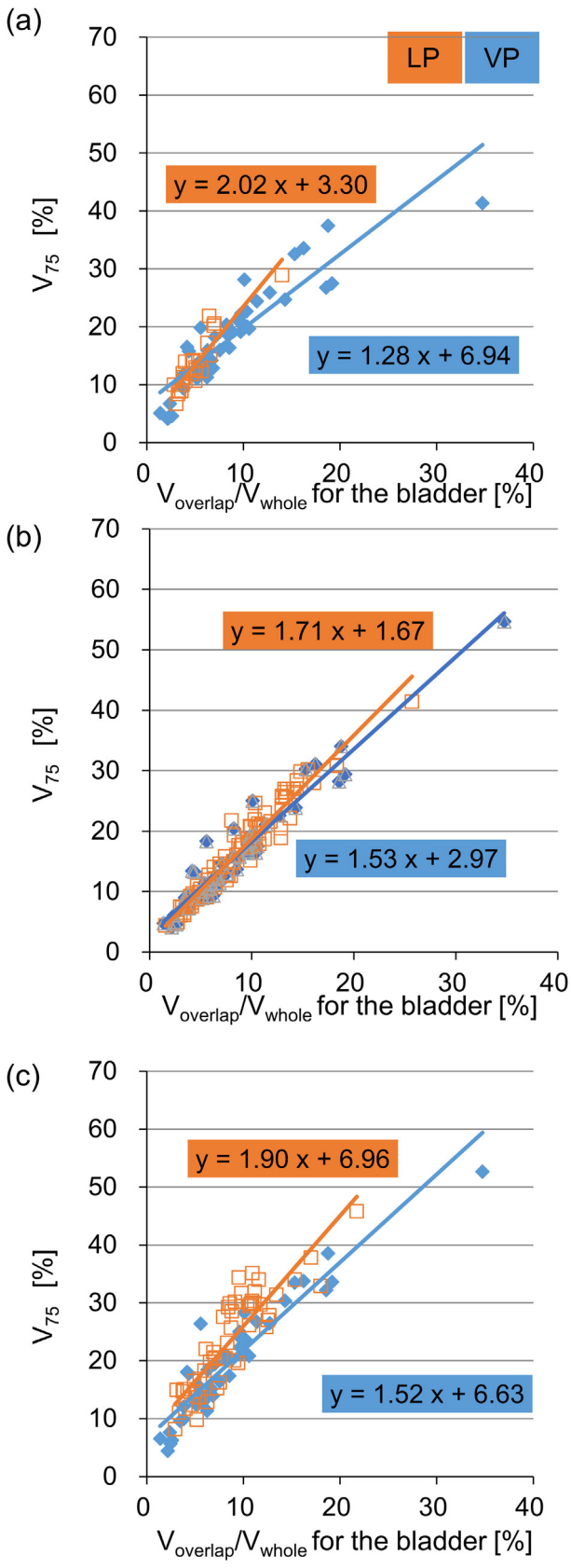

Fig. 2. Relationship between V_{75} and $V_{overlap}/V_{whole}$ of the bladder at institutes A (a), B (b), and C (c). The horizontal axis is $V_{overlap}/V_{whole}$ for the bladder. The vertical axis is V_{75} for the bladder. Blue and orange dots represent the doses in library plans (LP) and validated plans (VP), respectively. Each solid line is a linear regression line between each bladder dose and $V_{overlap}/V_{whole}$ for the bladder. Gray dots represent the doses in manual plans for validated cases.

Table 3
Correlation values between $V_{overlap}/V_{whole}$ and each dosimetric value for library plans (LP) and validation plans (VP) using each model.

OAR	Institute	V_{50} LP	VP	V_{75} LP	VP	V_{90} LP	VP
Rectum	A	0.76	0.93	0.89	0.97	0.99	0.98
	B	0.41	0.96	0.78	0.98	0.78	0.99
	C	0.48	0.57	0.50	0.73	0.34	0.63
Bladder	A	0.78	0.74	0.91	0.90	0.91	0.94
	B	0.87	0.85	0.97	0.96	0.99	0.99
	C	0.83	0.76	0.88	0.93	0.90	0.97

Abbreviations: $V_{overlap}/V_{whole}$ ratio of overlap between OAR volume and planning target volume to the whole organ volume, V_{50} volume ratio receiving 50% of the prescribed dose, V_{75} volume ratio receiving 75% of the prescribed dose, V_{90} volume ratio receiving 90% of the prescribed dose.

Table 4
The rata of slopes of linear regression lines between $V_{overlap}/V_{whole}$ and each dosimetric value for library plans (LP) and validation plans (VP) using each model.

	Institute	V_{50}	V_{75}	V_{90}
Rectum	A	0.83	0.92	1.26
	B	1.16	0.94	1.01
	C	0.51	0.79	0.91
Bladder	A	0.63	0.64	0.71
	B	0.70	0.88	1.04
	C	0.67	0.79	0.87

Abbreviations: $V_{overlap}/V_{whole}$ ratio of overlap between OAR volume and planning target volume to the whole organ volume, *OAR* organ at risk, V_{50} volume ratio receiving 50% of the prescribed dose, V_{75} volume ratio receiving 75% of the prescribed dose, V_{90} volume ratio receiving 90% of the prescribed dose.

The averages of each dosimetric parameter in VP were inconsistent with those in LP in Table 2. Generally, in the cases which $V_{overlap}/V_{whole}$ is small, it is easy to reduce organs' dose. As shown in Table 1, the organs' volume and $V_{overlap}/V_{whole}$ in LP is different from those for VP at each institute. Therefore, the averages of each dosimetric parameter in VP were inconsistent with those in LP. The OAR dose in KBP depended on the $V_{overlap}/V_{whole}$ for the OAR in each model, we suggest selecting optimal KBP models for each case. According to the formulas of LP and VP in Fig. 1, $V_{overlap}/V_{whole}$ for the rectum was over 20%, and V_{75} of the rectum was over 30% in the models at Institutes A and B. Thus, when a V_{75} value of less than 20% is required for cases in which $V_{overlap}/V_{whole}$ for the rectum is 20%, the model created at Institute C is effective. According to the regression line formulas for VP in Fig. 1, when $V_{overlap}/V_{whole}$ for the rectum was 5%, the V_{75} values for LP and VP at Institute A were the smallest among the three institutes. Therefore, in cases with a $V_{overlap}/V_{whole}$ value of 5% for the rectum, the model created at Institute A is effective. To select the optimal model from multiple models, characterization of OAR dose for LP in terms of $V_{overlap}/V_{whole}$ for the OAR should be evaluated.

Wang et al.[21] suggested a method to evolve KBP models in which plans with lower doses to OARs were re-registered to improve the models and reduce the doses to the OARs by several percent. The results of this study indicate that differences in LP greatly impact VP. The analysis of V_{75} for the rectum in VP at Institutes A and B (Fig. 1(b)) showed that when $V_{overlap}/V_{whole}$ was 10%, the rectal doses calculated by each regression formula were 16.9% and 22.3% at institutes A and B, respectively, although there were small differences between the PTV values of the two institutions. To improve the KBP model, plans with lower doses to OARs (instead of the original plans) should be re-registered to the model.

Moreover, we investigated whether LP could predict the results for KBP even if the model was trained by the minimum number of cases in LP.[19] Figs. 1 and 2 show that at institution A, which had the minimum number of 20 cases, the regression lines for LP coincide with those for VP in comparison with the results at other institutions. This indicates that even if the number of LP is 20, the calculation results of KBP can be predicted by LP, i.e., the number of the cases used to train the model was independent of the KBP prediction.

There are two main OARs for the prostate: the rectum and bladder. These two OARs have different limitations to calculate the dose distribution in inverse planning. Planners should focus on the high and medium dose regions of the rectum.[22] This study employed three institutions' original plan designs for the rectum. The plan design of Institute C reduced the dependence of rectal dose on $V_{overlap}/V_{whole}$; therefore, the slopes of its regression lines for LP (Fig. 1) were the smallest among the three institutions. The plan design affected characterizations for VP, so institute C's regression slopes of VP were also the smallest among the three institutions. In contrast, the relationships of the regression lines for all dose–volume parameters between LP and VP were similar among the three institutions. In VP, the variation of the slopes for the bladder (Fig. 2 and Table 3) was smaller than that for the rectum across all three institutions.

Chang et al. set the upper objectives manually to improve KBP with RapidPlan.[23,24] In this study, the upper objectives (except line objectives) were set automatically at each institution to decrease high-dose regions in the rectum because the maximum dose is more important in serial organs such as the rectum. The upper objectives were decided at each institute to suit each institute's dose constraints. When the models created by different institutes are shared, it is of particular concern that upper objectives be set according to various institutional constraints. In RapidPlan, the line objectives are placed horizontally in the overlap region between the PTV and OARs to prevent underdosing the PTV,[25] which increases the high-dose volume.[7] These results indicate that some objectives (but not line objectives) are required to attain ideal dose distributions with RapidPlan. To reduce dose variation between planners, the RapidPlan system should be improved to attain ideal dose distributions with only line objectives.

5. Conclusion

Dosimetric characterizations of the rectum and bladder using LP and VP in KBP were analyzed. Performance in terms of reducing dosimetric variations to OARs depends on each model. Sorting doses to OARs in LP in terms of $V_{overlap}/V_{whole}$ was an efficient method to predict the performance of VP.

Conflict of interest

None declared.

Financial disclosure

This study was supported by JSPS KAKENHI Grant (17K15817) to Yoshihiro Ueda. The authors gratefully acknowledge the support provided by the Japanese Society of Radiological Technology (JSRT) Research Grant (2019, 2020).

Acknowledgements

We thank Richard Lipkin, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

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